SAINT AGNES MEDICAL CENTER
CLINICAL RESEARCH CENTER
Fresno, California

STANDARD OPERATING PROCEDURES
Institutional Review Board

Date Effective: April 26, 2001 Index No. R – 1215
Date Last Revised: 4/11
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SUBJECT: **EXPEDITED REPORTING OF UNANTICIPATED PROBLEMS AND UNEXPECTED ADVERSE DEVICE EFFECTS TO THE IRB**

1. PURPOSE

Outline the policy and procedure for expeditiously reporting locally occurring unanticipated problems and unanticipated adverse device effects to the Institutional Review Board (IRB), and to describe the reporting by the study Sponsor of non-local IND safety reports to the IRB.

2. SCOPE

This applies to all research involving human subjects approved by the Institutional Review Board (IRB) in which drugs, biological materials or devices are being evaluated and are not exempt from federal regulations.

3. POLICY

- For investigational drug studies, federal regulations (21 CFR 312.64(b)) require that the Investigator promptly report to the Sponsor any adverse event that may be reasonably regarded as caused by, or probably caused by, the investigational drug. However, if the adverse event is *alarming*, the investigator shall report the adverse event immediately after the Investigator's learning of the event to the Sponsor. Federal regulations (21 CFR 312.66) also require that the Investigator will promptly report to the IRB all *unanticipated problems* involving risks to human subjects or others (see definition below) - this includes all adverse drug reactions that are clinically s*erious and unexpected* in terms of nature, severity or frequency*.* Unexpected fatal or life-threatening experiences associated with the use of the investigational drug should be reported immediately (within 24 hours of the Investigator's learning of the event).

- For investigational device studies, federal regulations (21 CFR 812.150) require that the Investigator submit to the IRB and the Sponsor a report of any *unanticipated adverse device effect* (see definition below) occurring during an investigation as soon as possible, but no later than 10 working days after the investigator first learns of the effect. Additionally, regardless of attribution, the Investigator will report to the IRB and

4. KEY DEFINITIONS

4.1 DEFINITIONS APPLICABLE TO DRUG STUDIES:

Adverse Event (or Adverse Experience) means any untoward (i.e., unfavorable, negative or harmful) medical occurrence associated with the use of a drug in humans, without regard to causality.

Suspected Adverse Reaction means any adverse event for which there is a **reasonable possibility** that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality then adverse reactions, which means any adverse event caused by a drug.

Adverse Reaction means any adverse event **caused by** a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Serious means any adverse event or suspected adverse reaction which results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected means an adverse event or suspected adverse reaction which is not listed in the Investigator Brochure or whose specificity or severity is not consistent with the Investigator Brochure; or that is not consistent with the risk information described in the general investigational plan when an Investigator Brochure is not required.

An Unanticipated Problem is an adverse event, incident or outcome that meets **all** of the following criteria:

(1) UNEXPECTED (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.

(2) SUSPECTED in that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

(3) SERIOUS because it suggests that the research places subjects or others at a **greater risk** of harm (including physical, psychological, economic or social harm) than was previously known or recognized, and would most likely require

a significant, usually safety-related change, in the protocol, informed consent or Investigator Brochure.

[See the Appendix for the OHRP's Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem.]

4.2 DEFINITIONS APPLICABLE TO INVESTIGATIONAL DEVICES:

An Unanticipated Adverse Device Effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5. PROCEDURE

5.1 EXPEDITED REPORTING OF LOCAL PROBLEMS/EVENTS:

It is the local Investigator's responsibility to report all of the following to the IRB Office and the Sponsor within 24 hours of learning of the following:

- For Drugs and Biologics: Any unanticipated problems, including any suspected adverse reaction that are serious and unexpected and suspected;

- For Devices: Any unanticipated adverse device effect. Moreover, the Investigator will report to the IRB and Sponsor within 24 hours of learning of any **death or life-threatening event**, regardless of attribution and whether or not the Investigator or Sponsor initially considers it to be an "Unanticipated Adverse Device Effect".

Investigators should use either the IRB's 'Report of a a Serious Adverse Event or an Unanticipated Problem' form or the 'Report of an Unexpected Adverse Device Effect' form to provide information to the IRB. Event follow-up information should be provided within five days of the Investigator's learning of the event or as soon as available.

The IRB Coordinator will review the expedited report upon receipt and will forward it to the Research Director and the IRB Administrative Subcommittee. All local unanticipated problems and unanticipated adverse device effects will be reported to the full Board for review and possible action.

If in the opinion of the IRB, with or without other (i.e., external) expert opinion, an unanticipated problem or an unexpected adverse device effect represents a significant risk to the rights and welfare of study subjects, the IRB may temporarily suspend research activities [IRB SOP R-1214]. In that event, the Chairperson will inform both the Investigator and the Sponsor. Contingent on review of all parties, a decision will be made to continue the research as planned, to continue as appropriately modified or to terminate.

5.2 REPORTING OF NON-LOCAL SAFETY REPORTS TO THE SAMC IRB :

In multi-center clinical trials, an unanticipated problem or unexpected adverse device effect occurring at external investigational sites must be reported to the SAMC IRB **only if the unanticipated problem poses risks to SAMC Investigator trial participants.**

A brief summary of these non-local safety reports (either sent as individual reports or an aggregate analysis) will be reviewed by the IRB Administrative Subcommittee and will be subsequently reported to the full Board under 'Summary of Expedited Actions'. The complete non-local safety report(s) will be made available to the full Board if requested.

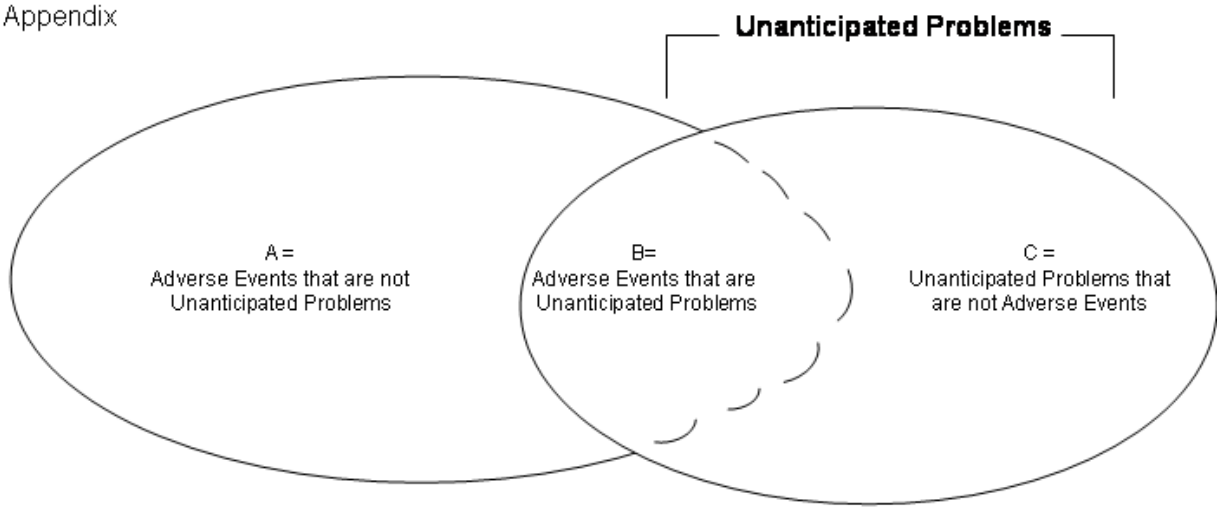
5.3 Reporting Non-Serious Adverse Events and Serious Expected Adverse Events

Although these are not reportable to the IRB, it is the Investigator's responsibility to report them to the Sponsor in accordance with the protocol.

REGULATORY REFERENCES:

45 CFR 46	Protection of Human Subjects ("The "Common Rule")
21 CFR 56.115	IRB Records
21 CFR 312.64	Investigator Reports
21 CRF 812.150	Investigator Reports
ICH E6	Good Clinical Practice: Consolidated Guidance (April 1996)
FDA Guidance	"Adverse Event Reporting to IRBs – Improving Human Subject Protection" (January 2009)
FDA Guidance	"Safety Reporting Requirements for INDs and BA/BE Studies" (September 2010)
OHRP Guidance	"Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or others and Adverse Events" (January 15, 2007)
CA H&S Code 24170-24179.5	Protection of Human Subjects in Medical Experimentation
CA H&S Code 111515-111545	Experimental Use of a Drug
CAMH RI.2.180	Protection of Research Subjects

Appendix



Do not report A **Report B and C**

To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the AE unexpected?
- Is the AE related or possibly related to participation in the research?
- Does the AE suggest that the research places subjects or others at a greater risk of harm than was previously known?

If the answer to all three questions is yes, then the adverse event is an unanticipated problem and should be reported to the Sponsor and the IRB.

CR SOP R-SM-404 5/08

Adopted from OHRP's "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events", January 15, 2007.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem